

WHAT IS CLAIMED IS:

1 1. A nucleic acid encoding a MCOLN1 polypeptide, wherein a mutation of a
2 *MCOLN1* gene encoding the MCOLN1 polypeptide results in a defect in expression of a
3 functional MCOLN1, wherein the nucleic acid shares at least about 95% sequence identity with a
4 corresponding sequence from SEQ ID NO: 1 or SEQ ID No: 2.

1 2. The nucleic acid of claim 1, wherein the mutation is selected from the
2 group consisting of an insertion in the gene, a deletion of the gene, a truncation of the gene, a
3 nonsense mutation, a frameshift mutation, a splice-site mutation, and a missense mutation.

1 3. The nucleic acid of claim 1, wherein the mutation is selected from the
2 group consisting of:

- 3 (a) an A to G substitution at position 5534 (SEQ ID NO:1);
4 (b) a deletion from nucleotide 511 to nucleotide 6944 (SEQ ID NO:1);
5 (c) an insertion of T between nucleotide numbers 1334 and 1335 (SEQ ID NO:2);
6 (d) a deletion of CTT 1346-1348 (SEQ ID NO:2);
7 (e) an A to G substitution a position 9107 (SEQ ID NO:1);
8 (f) a G to T substitution at position 1461 (SEQ ID NO:2);
9 (g) a C to T substitution at position 429 (SEQ ID NO:2);
10 (h) a G to T substitution at position 1209 (SEQ ID NO:2);
11 (i) a CC deletion at 598-599 (SEQ ID NO:2); and
12 (j) a C to T substitution at position 639 (SEQ ID NO:2).

1 4. The nucleic acid of claim 1, wherein the defect in expression of a
2 functional MCOLN1 results in development of mucopolipidosis IV.

1 5. The nucleic acid of claim 1, which encodes a MCOLN1 polypeptide
2 having an amino acid sequence at least about 95% identical to SEQ ID NO:3.

1 6. The nucleic acid of claim 5, wherein the polypeptide has an amino acid
2 sequence as depicted in SEQ ID NO:3.

1 7. The nucleic acid of claim 6 which has a nucleotide sequence as depicted in
2 SEQ ID NO:1 or SEQ ID NO:2.

1 8. A MCOLN1 polypeptide which has an amino acid sequence at least about
2 95% identical to SEQ ID NO: 3.

1 9. MCOLN1 polypeptide of claim 8, wherein the polypeptide has the amino
2 acid sequence of SEQ ID NO:3 comprising a mutation selected from the group consisting of
3 deletion of residue 408, deletion of residues 454 to 469; a Val to Leu substitution at residue 446;
4 an Arg to X[?] substitution at residue 102; an Asp to Thr substitution at residue 362; and an Arg
5 to X[?] substitution at residue 172.

1 10. The MCOLN1 polypeptide of claim 8 which has an amino acid sequence
2 as depicted in SEQ ID NO:3.

1 11. An antibody that binds specifically to the MCOLN1 polypeptide of claim
2 8.

1 12. A method for detecting a genetic mutation associated with a mucopolidosis
2 in a mammal, which method comprises detecting a mutation in a gene for MCOLN1, wherein the
3 gene for MCOLN1 has a sequence at least 95% identical to SEQ ID NO:1.

1 13. The method according to claim 12, wherein the mutation is selected from
2 the group consisting of an insertion in the gene, a deletion of the gene, a truncation of the gene, a
3 nonsense mutation, a frameshift mutation, a splice-site mutation, and a missense mutation.

1 14. The method according to claim 13, wherein the mutation is selected from
2 the group consisting of:

- 3 (a) an A to G substitution at position 5534 (SEQ ID NO:1);
- 4 (b) a deletion from nucleotide 511 to nucleotide 6944 (SEQ ID NO:1);
- 5 (c) an insertion of T between nucleotide numbers 1334 and 1335 (SEQ ID NO:2);
- 6 (d) a deletion of CTT 1346-1348 (SEQ ID NO:2);
- 7 (e) an A to G substitution a position 9107 (SEQ ID NO:1);
- 8 (f) a G to T substitution at position 1461 (SEQ ID NO:2);
- 9 (g) a C to T substitution at position 429 (SEQ ID NO:2);
- 10 (h) a G to T substitution at position 1209 (SEQ ID NO:2);
- 11 (i) a CC deletion at 598-599 (SEQ ID NO:2); and
- 12 (j) a C to T substitution at position 639 (SEQ ID NO:2).

1 15. The method according to claim 12, wherein the mucopolipidosis is
2 mucopolipidosis IV.

1 16. A method for diagnosing a mucopolipidosis, which method comprises
2 detecting a mutation in a gene for MCOLN1 that results in a defect in expression of a functional
3 MCOLN1, wherein the gene for MCOLN1 has a sequence at least 95% identical to SEQ ID
4 NO:1.

1 17. The method according to claim 16, wherein the mutation is selected from
2 the group consisting of an insertion in the gene, a deletion of the gene, a truncation of the gene, a
3 nonsense mutation, a frameshift mutation, a splice-site mutation, and a missense mutation.

1 18. The method according to claim 17, wherein the mutation is selected from
2 the group consisting of:

- 3 (a) an A to G substitution at position 5534 (SEQ ID NO:1);
4 (b) a deletion from nucleotide 511 to nucleotide 6944 (SEQ ID NO:1);
5 (c) an insertion of T between nucleotide numbers 1334 and 1335 (SEQ ID NO:2);
6 (d) a deletion of CTT 1346-1348 (SEQ ID NO:2);
7 (e) an A to G substitution a position 9107 (SEQ ID NO:1);
8 (f) a G to T substitution at position 1461 (SEQ ID NO:2);
9 (g) a C to T substitution at position 429 (SEQ ID NO:2);
10 (h) a G to T substitution at position 1209 (SEQ ID NO:2);
11 (i) a CC deletion at 598-599 (SEQ ID NO:2); and
12 (j) a C to T substitution at position 639 (SEQ ID NO:2).

1 19. The method according to claim 16, wherein the mucopolipidosis is MLIV.

1 ~~20.~~ A method for predicting the likelihood of developing MLIV comprising
2 detecting a mutation in a gene for MCOLN1 that results in a defect in expression of a functional
3 MCOLN1, and determining that there is a likelihood of developing MLIV if the mutation is
4 present, wherein the gene for MCOLN4 has a sequence at least 95% identical to SEQ ID NO:1.

1 21. The method according to claim 20, wherein the mutation is selected from
2 the group consisting of an insertion in the gene, a deletion of the gene, a truncation of the gene, a
3 nonsense mutation, a frameshift mutation, a splice-site mutation, and a missense mutation.

1 22. The method according to claim 21, wherein the mutation is selected from
2 the group consisting of:

- 3 (a) an A to G substitution at position 5534 (SEQ ID NO:1);
4 (b) a deletion from nucleotide 511 to nucleotide 6944 (SEQ ID NO:1);

- 5 (c) an insertion of T between nucleotide numbers 1334 and 1335 (SEQ ID NO:2);
- 6 (d) a deletion of CTT 1346-1348 (SEQ ID NO:2);
- 7 (e) an A to G substitution a position 9107 (SEQ ID NO:1);
- 8 (f) a G to T substitution at position 1461 (SEQ ID NO:2);
- 9 (g) a C to T substitution at position 429 (SEQ ID NO:2);
- 10 (h) a G to T substitution at position 1209 (SEQ ID NO:2);
- 11 (i) a CC deletion at 598-599 (SEQ ID NO:2); and
- 12 (j) a C to T substitution at position 639 (SEQ ID NO:2).

1 23. A kit for detecting a genetic mutation in a gene for MCOLN1 that results
2 in a defect in expression of a functional MCOLN1, comprising an oligonucleotide that
3 specifically hybridizes to or adjacent to a site of a mutation of the gene for MCOLN1 that results
4 in a defect in expression of a functional MCOLN1, wherein the gene for MCOLN1 has a
5 sequence at least 95% identical to SEQ ID NO:1.

1 24. The kit according to claim 23, wherein the oligonucleotide is a labeled
2 probe having a sequence corresponding to the sequence of the gene encoding MCOLN1 at the
3 site of the mutation, whereby hybridization of the probe is indicative of the presence of the
4 mutation.

1 25. The kit according to claim 23, wherein the oligonucleotide hybridizes to a
2 first site adjacent to the site of the mutation, further comprising a second oligonucleotide that
3 specifically hybridizes to a second site adjacent to the site of the mutation, wherein the second
4 site is on the opposite strand relative to the first site, and oriented relative to the first site such
5 that both sites flank opposite sides of the site of the mutation, whereby the first and second
6 oligonucleotides serve as primers for PCR amplification of the site of the mutation.

1 26. The kit according to claim 23, wherein the mutation is selected from the
2 group consisting of an insertion in the gene, a deletion of the gene, a truncation of the gene, a
3 nonsense mutation, a frameshift mutation, a splice-site mutation, and a missense mutation.

1 27. The kit according to claim 26, wherein the mutation is selected from the
2 group consisting of:

- 3 (a) an A to G substitution at position 5534 (SEQ ID NO:1);
4 (b) a deletion from nucleotide 511 to nucleotide 6944 (SEQ ID NO:1);
5 (c) an insertion of T between nucleotide numbers 1334 and 1335 (SEQ ID NO:2);
6 (d) a deletion of CTT 1346-1348 (SEQ ID NO:2);
7 (e) an A to G substitution a position 9107 (SEQ ID NO:1);
8 (f) a G to T substitution at position 1461 (SEQ ID NO:2);
9 (g) a C to T substitution at position 429 (SEQ ID NO:2);
10 (h) a G to T substitution at position 1209 (SEQ ID NO:2);
11 (i) a CC deletion at 598-599 (SEQ ID NO:2); and
12 (j) a C to T substitution at position 639 (SEQ ID NO:2).

1 28. A kit for detecting a genetic mutation in a gene for MCOLN1 that results
2 in a defect in expression of a functional MCOLN1 polypeptide, comprising the antibody of claim
3 11 and a detector of antibody binding.

1 29. A method of treating a mucopolipidosis or ion channel defect in a subject
2 suffering from mucopolipidosis or ion channel defect, which method comprises administering an
3 amount of a vector that expresses a nucleic acid encoding functional MCOLN1 effective to
4 express a functional level of MCOLN1 into cells of the subject, wherein at least the functional
5 MCOLN1 has an amino acid sequence that is at least about 95% identical to SEQ ID NO:3.

1 30. The method according to claim 29 wherein the MCOLN1 has an amino
2 acid sequence as depicted in SEQ ID NO:3.

1 31. The method according to claim 29, wherein the mucopolipidosis results from
2 a mutation in a gene for MCOLN1 that results in a defect in expression of MCOLN1.

1 32. The method according to claim 29, wherein the mucopolipidosis is MLIV.

1 ~~33.~~ An expression vector comprising a gene encoding functional human
2 MCOLN1 operatively associated with a promoter, wherein the functional MCOLN1 has an
3 amino acid sequence that is at least about 95% identical to SEQ ID NO:3.

1 34. The expression vector of claim 33, wherein the functional MCOLN1 has
2 an amino acid sequence as depicted in SEQ ID NO:3.

1 35. A pharmaceutical composition comprising the expression vector of claim
2 33 and a pharmaceutically acceptable carrier or excipient.

1 36. A method of screening for a candidate compound that modulates activity
2 of MCOLN1, which method comprises detecting binding of MCOLN1 with a compound and
3 isolating the compound, wherein the functional MCOLN1 has an amino acid sequence that is at
4 least about 95% identical to SEQ ID NO:3.

1 37. The method according to claim 36, wherein the MCOLN1 is a mutant
2 form of MCOLN1.

1 38. The method according to claim 36, wherein the functional MCOLN1 has
2 an amino acid sequence as depicted in SEQ ID NO:3.
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